REMARKS/ARGUMENTS

Status of the claims

With entry of the instant amendment, claims 1, 8-10, 15 and 18 have been amended and claims 3-7 and 17 have been cancelled. Claims 1, 2, 8-16, 18, and 19 are therefore pending and under examination.

Cancellation of subject matter is without prejudice to revival for prosecution in a continuation or divisional application.

The amendments to the claims add no new matter. Support for the amendment to claim 1 can be found, *e.g.*, in claim 8 as filed. The amendments to claims 9, 10, 15 and 18 delete reference to cancelled claim 4. Claim 18 has also been amended to recite a therapeutically effective unit dose; support can be found, *e.g.*, at paragraph 73.

Rejection under 35 U.SC. § 112, second paragraph

Claim 17 is rejected as lacking insufficient antecedent basis and as improperly broadening the scope of the claim. In the interests of expediting prosecution of the current claims, claim 17 has been cancelled. The rejection is therefore obviated.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 7, and 9-17 are rejected as allegedly not enabled insofar as the claims relate to *in vivo* use. The claims are also rejected as allegedly not enabled for the scope as it relates to the inhibition of any virus. In the interests of facilitating prosecution, claim 1 has been amended to relate to human immunodeficiency virus. With regard to the allegation that the claims are not enabled for *in vivo* use, the specification teaches compounds that can be used for inhibition of viral replication and how such compounds can be formulated and administered *in vivo* (see, *e.g.*, paragraphs 58-76). Applicants provide herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Robert Shoemaker ("Shoemaker Declaration") that provides additional evidence that the specification properly enables the *in vivo* use of the compositions.

In his Declaration, Dr. Shoemaker presents data showing that an exemplary compound having a structure as claimed inhibits HIV-1 replication *in vivo* using the SCID-hu mouse model that was developed for the study of HIV-1 pathogenesis *in vivo*. First, Dr. Shoemaker describes the model, which is an art-accepted model used for the evaluation of anti-HIV compounds. The model is constructed by transplantation of interactive human lymphoid organs into immunodeficient CB-17-scid mice. The SCID-hu model has been optimized by use of conjoint implants of human fetal thymus and liver to create the SCID-hu Thy/Liv mouse. These organs fuse, become vascularized, and grow when implanted beneath the kidney capsule of recipient mice. A stable organ termed "Thy/Liv" is thus established with histologically normal cortical and medullary compartments that are capable of multilineage human hematopoiesis and generating a continuous source of human $CD4^+$ T cells for 6-12 months. The implants support viral replication after inoculation of HIV-1 by direct injection and thymocyte depletion occurs with some viral isolates within 3-5 weeks. This depletion includes loss of $CD4^+CD8^+$ immature cortical thymocytes and a decrease in the CD4/CD8 ratio in the thymic medulla. Dr. Shoemaker further notes that administration of nucleoside (AZT, ddl, 3TC) and nonnucleoside (nevirapine) reverse transcriptase inhibitors to these mice has shown dose-dependent inhibition of HIV-1 replication (and protection of $CD4^+$ cells) within the implanted human tissue, thus providing further validation of the model. In addition, the model has been used for the evaluation of numerous new classes of anti-HIV compounds.

The data presented in the Shoemaker Declaration were obtained using a representative pentavalent antimony-containing small molecule of the invention (designated NSC 13778). Dr. Shoemaker indicates that the compound has an EC_{50} of 1 μM and selectivity index of greater than 426 in CEM-SS cells infected with the HIV-1 isolated RF. Furthermore, a toxicity study of NSC 13778 in the mouse model demonstrated that twice-daily subcutaneous injections of NSC 13778 at 2-60 mg/kg/day for 21 days caused no apparent toxicity or body weight loss (Figure 1 of the Shoemaker Declaration). Treatment also did not cause thymocyte depletion or perturbations in thymocyte subpopulations except for a minor decrease in CD4/CD8 ration (from 2.9 to 2.0) at 60 mg/kg/day.

The Shoemaker Declaration describes the following experiments. A total of 45 mice were evaluated in the antiviral efficacy experiments. Thy/Liv mice were inoculated with HIV-1 by direct injection of 1,250 $TCID_{50}$ into each Thy Liv/implant. Mice were divided into seven groups (A-G) of seven animals each. Group A through F mice were inoculated with virus and group G mice were mock-inoculated. Groups A, B, and C were treated with NSC 13778. The drug 3TC was administered to animals in group D as a positive control (it is known to inhibit HIV-1 viral infection); vehicle alone (group E) was used as a negative control. Mice in groups F and G were not treated with either drug or vehicle. All mice were dosed by subcutaneous injection (150 μL per dose) twice-daily throughout the treatment course. The amounts administered were: 60 mg/kg/day NSC13778 (group A), 20 mg/kg/day NSC13778 (group B), 6 mg/kg/day NSC13778 (group C), 30 mg/kg/day 3TC (group D), and vehicle only, 0.05 M NaOH, (group E). Groups A-G were treated for 1 day, inoculated with virus or mock-inoculated and subsequently treated for 21 days, all as described above. At the end of the 21 days of treatment, Thy/Liv implants were surgically excised from mice in groups A through G in order to examine the effect of NSC 13778 on HIV-1 replication by measuring levels of p24-Gag and HIV-1 RNA. Four mice (one each in Groups B, C, F, and G) were not included in the analyses, three because of poor implant quality and one because of an abnormal cell profile.

Post-excising, implant thymocyte samples were obtained and either lysed for p24 analysis or stored and subsequently processed by standard methods for RNA isolation and analysis. The levels of p24 were measured by standard ELISA protocols. The levels of RNA were detected using the VERSANT™ HIV-1 RNA 3.0 Assay (Bayer Diagnostics, Norwood, Massachusetts). MHC class I detection was performed using fluorescently labeled anti-CD4, anti-CD8, anti-CD3 and anti-CD195 antibodies in a standard FACS analysis.

Dr. Shoemaker next describes the results. Untreated, HIV-1 infected mice (Group E) had means of 590 ± 87 pg p24 and 5.8 ± 0.15 $\log_{10}$ copies HIV-1 RNA per 10^6 implant cells and 8.6 ± 1.1% Gag-$p24^+$ thymocytes at 21 days after inoculation. These untreated mice also exhibited a 3.1-fold increase in MHC class I expression on $CD4^+CD8^+$ immature cortical thymocytes. Substantial reductions in $CD4^+CD8^+$ thymocytes (from 82% to 33%), CD4/CD8

ratio (from 1.7 to 0.67) and thymocyte viability (from 83% to 52%) in infected compared to mock-infected implants also were observed at 21 days after virus inoculation.

Thy/Liv mice that were treated with NSC 13778 at 60 mg/kg/day exhibited statistically significant reductions in p24, from 590 to 210 pg p24 per 10^6 cells (Figure 2 of the Shoemaker Declaration). The 60 mg/kg/day treatment also reduced the HIV-1 viral RNA from 5.8 $\log_{10}$ to 4.9 $\log_{10}$ copies per 10^6 cells and Gag-$p24^+$ thymocytes from 8.6% to 4.9% as compared to non-NSC 13778 treated, HIV-1 infected controls (also Figure 2 of the Shoemaker Declaration), however, there were no significant reductions in MHC class I expression on $CD4^+CD8^+$ thymocytes from NSC 13778-treated mice compared to implants from untreated, HIV-1 infected control mice. Treatment with NSC 13778 did not protect thymocytes from virus-mediated depletion.

In summary, the data presented by Dr. Shoemaker demonstrate dose-related inhibition of HIV replication, as assessed by p24 viral core antigen levels and HIV RNA levels, in response to treatment with NSC 13778 using an art-accepted *in vivo* model. The studies in the Shoemaker Declaration therefore provide additional evidence that the specification properly enables one of ordinary skill in the art to use the compound of the invention *in vivo* to inhibit proliferation of a virus.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 7, 8, 18, and 19 are rejected as allegedly anticipated by Wasfi and Johnson, in *Recent Res. Devel. Inorganic Chem*:2115-129, 2000 ("Wasfi & Johnson"). The Examiner describes Wasfi & Johnson as teaching a method of inhibiting viral replication using various compounds, including the most basic compound of the series, $C_6H_4SbO_3H_2$. The Examiner alleges that Wasfi & Johnson therefore anticipate the current claims. Applicants traverse this rejection. The Examiner's characterization of the disclosure of Wasfi & Johnson is inaccurate. Wasfi & Johnson fail to teach each and every element of the claims.

First, the current claims do not encompass what the Examiner describes as the basic compound, $C_6H_4SbO_3H_2$. Claim 1 recites the proviso that at least one of R^{14}, R^{15} and R^{16} is other than H. Accordingly, this excludes $C_6H_4SbO_3H_2$.

Furthermore, there is no teaching in Wasfi & Johnson that $C_6H_4SbO_3H_2$ has antiviral activity of any kind. The last paragraph of the first column of page 116 of Wasfi & Johnson indicates that a total of 30 compounds listed in Table 1 were tested for antiviral activity against HIV-1, herpes, and respiratory viruses. The structure $C_6H_4SbO_3H_2$ is one of these compounds. It is designated SHW43 in Table 1. There is no disclosure in Wasfi & Johnson that SHW 43 has any antiviral activity, however. Page 117 discloses that the redox potential of each active compound is listed in Table 2. Table 2 does not list SHW43. Nor do any of Tables 2, 3, and 5 (which show the results of the antiviral studies; see, the first paragraph of the Conclusions section on page 126) list SHW43 as having antiviral activity. Thus, Wasfi & Johnson do not disclose a method of inhibiting viral replication using a compound as set forth in the claims, nor do Wasfi & Johnson disclose a pharmaceutical formulation comprising a therapeutically effective unit dose of a compound set out in claim 1. Wasfi & Johnson therefore fail to anticipate the claims. It is respectfully requested that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 9, 15 and 17 are rejected as allegedly unpatentable over Wasfi & Johnson. The Examiner contends that although Wasfi & Johnson do not specifically teach *in vivo* administration of the compounds, it would have been obvious to use the compositions *in vivo*. Applicants respectfully traverse this rejection. Wasfi & Johnson fail to disclose *in vitro* inhibition of viral replication using a composition of the invention. Therefore, there is no basis for one of skill to select a composition as claimed with a reasonable expectation that the composition would inhibit viral replication *in vivo*. Accordingly, the rejection fails to establish a case that the claims are prima facie obvious. Applicants therefore request withdrawal of the rejection.

Claims 10-14 are rejected as allegedly unpatentable over Wasfi & Johnson in view of Hermans (*Biomedicine and Pharamcotherapy* 55:301-307, 2001). The Examiner

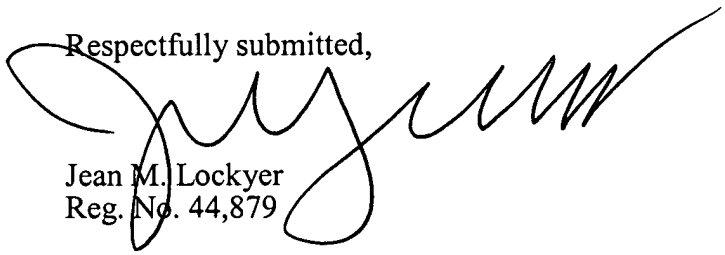
contends that it would have been obvious to use the currently claimed compositions in a combination therapy based on Hermans' teaching that it is desirable to include more than one class of anti-viral therapeutic agents for the treatment of HIV infection. Applicants respectfully traverse this rejection. The teachings of Wasfi & Johnson are defective for the reasons explained above. Hermans provides no disclosure that overcomes this deficiency. Accordingly, the claims are patentable over the combination of references. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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